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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,731	04/25/2001	John Smit	08106-004001	7587

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/743,731

Applicant(s)

SMIT, JOHN

Examiner

David J Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

- [1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 04, 2004 has been entered.
- [2] Claims 1-6 are pending in the application.
- [3] Applicant's amendment to the claims, filed December 19, 2003, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
- [4] Applicant's arguments filed December 19, 2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

- [6] Claim 1 is objected to in the recitation of "C. crescentus". In the interest of clarity, it is suggested that applicants replace the term with "Caulobacter crescentus".
- Appropriate correction is required.

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[7] Claim 1 is objected to in the recitation of "C-terminal". The term is grammatically incorrect and it is suggested that the claim be amended to replace "C-terminal" with "C-terminus" or to insert "end" following "C-terminal".

Claim Rejections - 35 USC § 112, First Paragraph

[8] In view of applicant's amendment to remove the limitation "a *Caulobacter crescentus* S-layer protein fragment incapable of adhesion to a *Caulobacter crescentus* cell surface", the new matter rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, as set forth in item [7] of the Office action mailed September 17, 2003 is withdrawn to the extent the rejection applies to this limitation. The amendment cancels the limitation of claim 1 that is not supported by the instant specification.

[9] Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claim 1 (claims 2-6 dependent therefrom) has been amended to recite "a *C. crescentus* S-layer protein fragment of at least about 120 amino acids... ..and no more than 405 amino acids of the C-terminal". Applicants' footnote at the bottom of page 4 of the response filed December 19, 2003, is noted. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation,

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or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". The examiner has carefully reviewed applicant's asserted support for amended claim 1. While the specification has implicit support for a fragment of the 120 C-terminal amino acids a *C. crescentus* S-layer protein, and a fragment of the 405 C-terminal amino acids of a *C. crescentus* S-layer protein, the examiner can find no support for a *C. crescentus* S-layer protein fragment having a range of amino acids of at least 120 to no more than 405 amino acids in the specification or claims as originally filed. In the event the examiner has inadvertently overlooked such support, applicant is invited to direct the examiner's attention to such support in the specification and/or claims as originally filed.

[10] Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 (claims 2-6 dependent therefrom) is drawn to a method for cleaving a genus of insoluble fusion proteins, wherein the genus of fusion proteins comprises a first component having a fragment of a genus of *C. crescentus* S-layer proteins of at least about 120 amino acids of the C-terminus and no more than about 405 amino acids of the C-terminus and a second component that is heterologous to *C. crescentus*. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a

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genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of C. crescentus S-layer proteins, i.e., SEQ ID NO:5. The genus of recited C. crescentus S-layer proteins encompasses species that are WIDELY variant in their structures. As such, the disclosure of the single representative species is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus. Given the lack of description of a representative number of C. crescentus S-layer proteins, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. Furthermore, it is noted that the genus of S-layer proteins as recited in claim 1 is limited to those that are considered to be "C. crescentus" S-layer proteins. The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a

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chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Also, MPEP § 2163 states (citing *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021), "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials". In this case, the specification fails to provide those characteristics that distinguish the subgenus of "C. crescentus S-layer proteins" from the larger genus of S-layer proteins that includes "C. crescentus" S-layer proteins, Caulobacter S-layer proteins, and S-layer proteins from all other sources. For the reasons stated above, the specification fails to provide adequate written description for the recited genus of C. crescentus S-layer proteins.

[11] The scope of enablement rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The examiner maintains the position that the specification, while being enabling for a method of cleaving an insoluble fusion protein comprising a first component having amino acids 622-1026, 690-1026, 784-1026, 892-1026 or 907-1026 of SEQ ID NO:5 and a second component that is heterologous to C. crescentus, does not reasonably provide enablement for the broad scope of claimed fusion proteins, particularly with respect to the broad scope of C. crescentus S-layer proteins as encompassed by the claims.

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Applicants argue the claims have been limited to the C-terminal 120-405 residues and have provided working examples of such in the specification and that the art provides adequate guidance for selecting a fragment of a C. crescentus S-layer protein for use in practicing the instant invention, citing Smit et al. as evidence thereof. Applicants' argument is not found persuasive.

Contrary to applicant's argument, it should be noted that the specification discloses only the fragments of amino acids 690-1026 (Examples 1-3, pages 15-17 of the specification) and amino acids 784-1026 (Example 4, pages 17-18 of the specification) of SEQ ID NO:5 as working examples of the first component of the recited fusion protein. However, it would not be undue experimentation to test those fragments that were not used as working examples, i.e., amino acids 622-1026, 892-1026, and 907-1026 of SEQ ID NO:5, for the appropriate biological activity in the claimed method (see MPEP 2164.08(b)).

Regarding the broad scope of recited C. crescentus S-layer proteins, it is noted that the recited C. crescentus S-layer protein is not limited by its structure. Thus, the claims encompass any C-terminal fragment within the scope of the claim from a C. crescentus microorganism, including (but not limited to) those S-layer proteins from C. crescentus microorganisms yet to be isolated and C. crescentus mutant strains generated by, e.g., UV radiation. In view of the state of the art, it is highly unpredictable as to whether such S-layer proteins would maintain the same characteristics as those fragments disclosed as working examples. Thus, undue experimentation would clearly be required to make the broad scope of methods, particularly with respect to the broad

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scope of C. crescentus S-layer proteins encompassed by the claims. Therefore, due to the broad scope of the claimed methods, the lack of guidance and working examples, the high degree of unpredictability, and the amount of experimentation required, the specification does not enable the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

[12] The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Smit et al. (US Patent 5,976,864; reference AA of the IDS filed May 24, 2001) in view of Nomellini et al. (*J Bacteriol* 179:6349-6354), Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, Inc., 1994; reference AR of the IDS filed November 13, 2002), and Better (US Patent 5,851, 802) is maintained for the reasons of record and the reasons stated below.

Applicant asserts it is the examiner's position that Nomellini et al. provide a "missing link" by teaching that full-length *Caulobacter crescentus* S-layer protein is resistant to solubilization. Applicant argues that the term "resistant to... solubilization" is not equivalent to insoluble and Nomellini et al. teach that full-length S-layer protein is generally soluble at low pH. Applicant argues that Nomellini et al. does not suggest any S-layer protein fragment recited in claim 1 that is insoluble at low pH. Applicant argues that Nomellini et al. does not provide a "missing link" and in view of the teaching of Nomellini et al. that full-length S-layer protein is generally soluble at low pH, this reference teaches away from using an S-layer protein or a fragment thereof as a fusion

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protein carrier. Applicant argues that the four cited references do not render obvious the claimed methods. Applicants' argument is not found persuasive.

Regarding the meaning of the term "resistant to... solubilization", it is noted that the term as quoted by Nomellini et al. is "refractory to... ..low-pH solubilization" and a standard definition of "refractory", according to the Fourth Edition of "The American Heritage® Dictionary of the English Language", 2000, Houghton Mifflin Company, is resistant to as in resistant to low-pH solubilization. It should also be noted that while applicant asserts the term "resistant to... solubilization" is not equivalent to insoluble, applicant provides no alternative explanation for the term and applicant's arguments cannot take the place of evidence (see MPEP 716.01(c) and 2145). As such, the term "refractory to... ..low-pH solubilization" has been interpreted as "resistant to... ..low-pH solubilization" in accordance with the standard definition of "refractory" as described above.

Regarding applicants' argument that Nomellini et al. teach that full-length S-layer protein is soluble at low pH, it is noted that this teaching (page 6351, right column) is directed to "wild-type" S-layer protein. The examiner has NOT referred to such a teaching in the previous Office action. Applicant is referred to the cited teachings of Nomellini et al. used by the examiner in the instant rejection – see pages 6-7 of the Office action mailed September 17, 2003. The examiner's cited teachings are directed to an S-layer shedding mutant, which lacks the "[smooth lipopolysaccharide] required for S-layer attachment" as disclosed at page 6352, left column, of Nomellini et al. It is the teachings of Nomellini et al. directed to the S-layer shedding mutant that were

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stated in a previous Office action, not teachings directed to the wild-type S-layer protein, as argued by applicant. Nomellini et al. teach that it is the S-layer shedding mutant that is "refractory to the low-pH solubilization". The teaching by Nomellini et al. that an S-layer protein from a shedding mutant is "refractory to the low-pH solubilization", and the teachings of Smit et al., who teach the use of S-layer shedding mutants in their fusion protein, specifically a fusion protein comprising amino acids 782-1026 of a Caulobacter crescentus shedding strain (strains CB15Ca5 and CB15Ca10) S-layer protein, one of ordinary skill in the art would have used such a fragment as taught by Smit et al. as a component of a fusion protein (see page 6 of the Office action mailed September 17, 2003). As such, contrary to applicant's assertion, Nomellini et al. do not teach away from the claimed invention and it is the examiner's position that, in view of the combined teachings of Smit et al., Nomellini et al., Ausubel et al., and Better, claims 1-6 would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[13] Status of the claims:

- Claims 1-6 are pending.
- Claims 1-6 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or

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informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

Patent Examiner

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[Signature]
03-30-04